脑岛在成瘾中的结构和功能异常*

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摘要 脑岛位于大脑外侧裂的深处，与情绪和内感受等多种心理功能有关。脑岛在成瘾中的结构变化和功能连接异常，表明了脑岛在成瘾中的作用，刺激脑岛区域干预成瘾的也逐渐成为研究者们关注的领域。未来的研究应该通过对脑岛进行精细分割和多种方法相结合来进一步考察脑岛在成瘾中的具体作用，并挖掘不同成瘾类型的共性和特性，以便更好开展基于脑的成瘾干预。

关键字：脑岛，成瘾，干预，功能连接，脑成像

人类的脑岛皮质（insular cortex, IC）位于大脑外侧裂的深处，是掌管着多种不同的认知和情绪功能的重要脑区(Mesulam & Mufson, 1982; Deen et al.,2011; Kelly et al., 2012)。脑岛与眶额叶皮质(orbitofrontal cortex, OFC)、前扣带回皮层(anterior cingulate cortex, ACC)、躯体感觉皮层以及包括杏仁核、苍白球和丘脑等在内的皮层下结构有重要的双向连接(McDonald, Shammah-Lagnado, Shi, & Davis, 1999; Shi & Cassell, 1998)。脑岛与多种成瘾行为相关，被称作人脑中“成瘾行为的隐秘岛”(Naqvi & Bechara, 2009)。

1. 脑岛的亚区结构和功能分化

近年来，利用电生理技术、正电子发射断层扫描（PET）和功能性磁共振成像（Functional magnetic resonance imaging, fMRI）等技术的活体成像和病变研究均表明，脑岛可以整合情感、认知和感觉运动系统，具有广泛的功能(Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Nieuwenhuys, 2012; Pavuluri & May, 2015)，是调节社会认知(Menon & Uddin, 2010)，同理心(Fan, Duncan, de Greck, & Northoff, 2011; Klimecki, Leiberg, Ricard, & Singer, 2014)，奖励驱动的决策(Bartra, McGuire, & Kable, 2013; Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015; Preuschoff, Quartz, & Bossaerts, 2008)，情绪(Kaczkurkin et al., 2017; Wise et al., 2017)以及躯体疼痛加工(Craig, 2003; Wiech, Jbabdi, Lin, Andersson, & Tracey, 2014)的枢纽。脑岛作为内感受加工系统的重要的神经中枢，在成瘾的形成、维持、戒断和复吸过程中具有极为关键的作用(Droutman, Read, & Bechara, 2015)。

脑岛作为一个参与众多大脑活动且具备广泛功能的特殊脑区，它的功能和结构都呈现出鲜明的异质性和前后分布式的特征。为更明确地体现脑岛功能和结构的分化，前人基于其功能和结构特征，对脑岛进行了亚区分割（如图 1 所示）。目前最成熟的两种脑岛分割，一种是根据构成细胞类型进行的解剖分割，将脑岛分为前腹侧的非颗粒皮层（agranular insula, AI）、

* 收稿日期：2020-07-23

重庆市自然科学基金（cstc2020jcyj-msxmX0215）和国家自然科学基金（31972906）。

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背后部的颗粒皮层（granular insula, GI）及中间的过渡层（dysgranular insula, DI）(Mesulam & Mufson, 1985)；另一种是基于静息态的功能连接分析（resting-state functional connectivity, rsFC），将脑岛分为三个功能亚区，分别是后脑岛（posterior insula cortex, PIC）、背侧前脑岛（dorsal anterior insula cortex, dAIC）以及腹侧前脑岛（ventral anterior insula cortex, vAIC）(Chang, Yarkoni, Khaw, & Sanfey, 2013)。我们可以发现，脑岛的结构分区和功能分区不完全重合，对此，目前尚且缺乏足够的研究为该差异产生的原因做出详实的阐述，但无论是基于结构还是功能，脑岛都呈现出前后分化的特征。前后脑岛的分化，主要体现在后脑岛更多地负责感觉运动，疼痛和语言处理等感知活动，而前脑岛则更多地涉及较高级的认知和执行力活动(Chang, Yarkoni, Khaw, & Sanfey, 2012)。且前后脑岛之间也在不断地进行信息交互，达到功能整合。一般来说，前脑岛与额叶的功能连接更强，后脑岛与顶叶的功能连接更强(Gasquoine, 2014)。

后脑岛向尾状核、丘脑和躯体感觉皮层发送投射信号(Shi & Cassell, 1998)，还接收来自顶叶、枕叶和颞叶联合皮层的输入信号，在疼痛、语言处理和感觉运动的整合中扮演着重要角色(Chang et al., 2013)。其颗粒区是感觉信息的多模式会聚区域，加工外感受信息（例如触摸、温度和疼痛）、内感受信息（例如躯体内脏感觉）(Craig, 2002, 2003)、听觉信息(Bamiou, Musiek, & Luxon, 2003)和前庭信息(Brandt, 1999)。

前脑岛（anterior insula cortex, aIC）向尾状核、伏隔核(nucleus accumbens, NAcc)和杏仁核发出投射信号，同时与基底外侧杏仁核(basolateral amygdala, BLA)和前边缘皮层相互连接(Gerfen & Clavier, 1979; Saper, 1982; Vertes, 2004)。前脑岛接收来自中背丘脑核的内侧部分和其他各种内侧丘脑核的输入，这些丘脑内侧核涉及到神经感觉的动机与情感功能(Krettek & Price, 1977; Van der Werf, Witter, & Groenewegen, 2002)。双侧前脑岛与前扣带回等边缘系统区域的连接，构成了"突显性检测"网络，即突显网络（salience network）(Seeley et al., 2007)。脑岛产生的感受状态决定了刺激的相对突显性，并按照优先顺序对刺激分配认知资源(Menon & Uddin, 2010; Uddin, 2015)，背外侧前额叶皮层（中央执行网络）接收前脑岛的突显信息并进行相应的处理，以此来控制如注意和工作记忆等认知过程(Menon & Uddin, 2010)，使我们注意并记住那些与自我稳定和情感感受相关的突显事件(Chun & Turkbrowne, 2007; Dolan, 2002)。总之，前脑岛从广阔的感官刺激中识别突显信息，并通过访问大脑的注意力和工作记忆资源促进突显信息的进一步加工(Mesulam & Mufson, 1985; Uddin, 2015)。

前后脑岛之间的交互，构成了脑岛功能的整合，并统一在了"内感受"的概念下 (Craig, 2002)。"内感受"是一个整合内部信号和外部刺激以维持内稳态的过程(Craig,2003)，经由脑岛由后向前进行。内感受信号首先到达后脑岛，这里被认为是初级内感受皮层，处理低水平的感觉特征(Harrison, Gray, Gianaros, & Critchley, 2010)。之后，这个信号被传递到前脑岛，在此，前脑岛将内感受信息整合到有意识的情绪感受中(Craig, 2009; Critchley et al.,

2004)，并向基底外侧杏仁核、伏隔核、前扣带回和 OFC 等投射信号，共同作用调节情感、动机、社交和执行功能(Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004)。

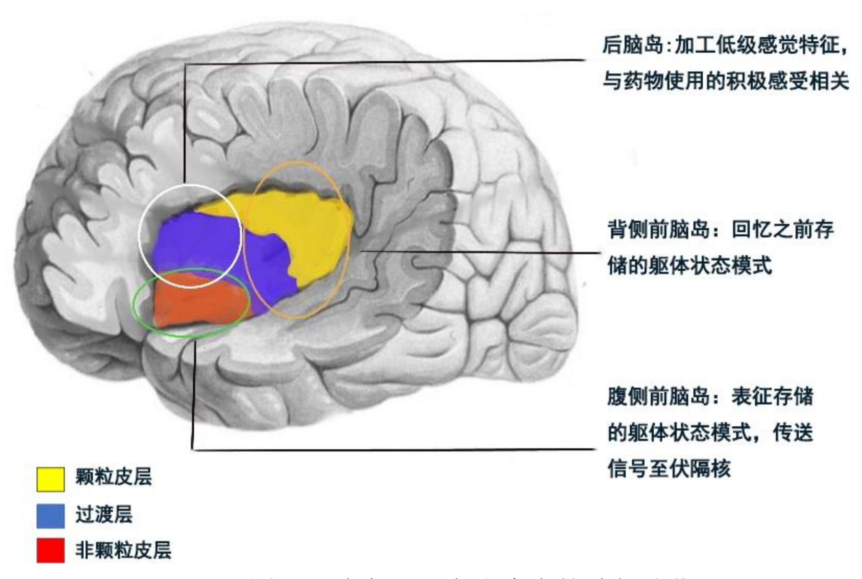


图 1　脑岛亚区在成瘾中的功能分化

正是由于脑岛的功能和结构分化的特点，我们可以通过对脑岛亚区的研究来进一步探索其在成瘾之中所起到的作用。在成瘾形成的初始阶段，脑岛参与了内感受药物效应与环境关联的情感学习过程。在药物使用过程中，与享乐体验相关的内感受信号首先到达后脑岛，引发后脑岛的初级内感受皮层的激活，使低级的感觉特征得到加工；接着，信号被传送到前脑岛，在此高级的内感受表征（或者说躯体状态模式）就到达意识层面并交给记忆相关区域（如海马）进行加工，接下来，当个体面临环境的药物刺激或线索时，背侧前脑岛就参与回忆之前存储的与药物经验有关的躯体状态模式，且通过腹侧前脑岛进行表征，并传送信号至伏隔核，从而激发成瘾者的主观渴求和药物寻求行为(Droutman, Read, & Bechara, 2015)。

2. 脑岛在成瘾中的结构和功能变化

2. 1　脑岛在成瘾中结构变化

脑岛作为支持内感受的关键脑区，在成瘾的所有主要方面都有所涉及并不奇怪。Naqvi 等人(Naqvi, Rudrauf, Damasio, & Bechara, 2007)首先注意到了脑岛在成瘾中的重要作用。他们发现，涉及脑岛损伤的吸烟者比控制组更容易吸烟上瘾；且能更容易地戒烟而不会复发，戒烟后也没有吸烟的冲动。后续脑损伤研究表明脑岛的损伤最能预测戒烟的成功，且被试戒烟的概率是脑岛未受损时的 5 倍 (Suner-Soler et al., 2012)。还有研究表明，脑岛损伤的吸烟者有更少的吸烟冲动(Abdolahi et al., 2017)，戒烟后的戒断症状更少，严重程度也更低(Abdolahi et al., 2015)。也有动物实验表明，暴露于尼古丁会改变脑岛突触的结构和功能，这似乎对持续吸烟行为的维持和尼古丁成瘾的发展至关重要(Naqvi, Gaznick, Tranel, & Bechara,

2014; Slotkin, 2002)。此外，随后的研究表明，邻近的基底神经节结构(如纹状体的壳核区)的损伤也会导致戒烟，Gaznick 等人(Gaznick, Tranel, McNutt, & Bechara, 2014)发现基底神经节损伤组、脑岛和基底神经节同时受损组比其他脑区损伤组的被试戒烟率明显更高、戒烟也更持久：在基底神经节损伤组中，37%的人在 12 个月的随访中没有复吸，而在脑岛和基底神经节同时受损组中，戒烟效果更好，该组中 75%的人在 12 个月的随访中没有复吸。大量证据表明，与不吸烟者相比，吸烟者脑岛的皮层厚度和灰质密度显著下降(Brody et al., 2004; Fritz et al., 2014; Stoeckel, Chai, Zhang, Whitfield-Gabrieli, & Evins, 2016)，尤其在左脑岛中，这种变化更为显著(Sutherland et al., 2016)。吸烟者左前岛延伸至额下叶和颞叶皮层的灰质密度较低且与每天吸烟量呈负相关(Stoeckel et al.，2016)，双侧前岛灰质体积与尼古丁依赖测试(FTND)得分呈负相关(Wang et al., 2019)，表明尼古丁的神经毒性作用对脑岛前部皮层的损害越严重，尼古丁的依赖程度越高。从年龄层面来看，与年轻吸烟者（20~29 岁）相比，较年长吸烟者（30~49 岁）的脑岛皮质密度变化更为明显(Hanlon et al., 2016)；而年轻吸烟者(16~21 岁)与不吸烟者相比，组间脑岛厚度无明显差异，但吸烟持续时间与右脑岛厚度呈负相关，吸烟依赖和吸烟冲动与右侧腹前岛皮质厚度呈负相关(Morales, Ghahremani, Kohno, Hellemann, & London, 2014)。这或许暗示我们，脑岛结构的变化可能是由于长期吸烟导致的。

尽管大多数研究认为脑岛与成瘾间关系的证据主要与尼古丁有关，但不可忽视的是，其他成瘾行为也被证明是脑岛影响的结果,且大都指向脑岛的体积和密度减小。例如，有脑岛损伤的缺血性中风患者在发病的前后更有可能停止使用鸦片，且这种影响在年轻患者中更为显著(Yousefzadeh-Fard et al.，2013)。大麻使用者的双侧脑岛皮质厚度下降(Lopez-Larson et al., 2011)；此外，与偶尔吸食大麻者相比，经常吸食大麻者左脑岛灰质体积减少，且该脑区的灰质体积的变化与被试在研究开始前 3 个月使用大麻的频率有关(Battistella et al.，2014)。与健康对照组相比，可卡因使用者脑岛皮质厚度更薄(Geng et al., 2017)，且可卡因依赖的时间越长，岛叶皮层的灰质体积减少越大(Barros-Loscertales et al., 2011)，而脑岛灰质体积的减少又与更大的可卡因使用冲动有关(Ersche et al., 2011)。海洛因依赖者脑岛右侧和后侧的灰质体积更小(Gardini & Venneri, 2011)，依赖兴奋剂的个体左脑岛的灰质显著减少(Ersche et al., 2013)。同样，甲基苯丙胺使用者双侧脑岛灰质密度减少(Schwartz et al., 2010)，且左脑岛受影响更大(Morales, Lee, Hellemann, O'Neill, London, & dependence, 2012)。饮酒也会引起脑岛灰质和白质的变化。酒精依赖患者的双侧脑岛灰质萎缩 (Yang et al., 2016)，与健康志愿者相比，酒精依赖者（年龄 22~56 岁）的双侧前脑岛体积减少了 10% (Senatorov et al., 2014)。从酒精成瘾治疗中招募的青少年被试的脑岛白质体积增大，并与 1 年内酗酒频率相关，右侧脑岛白质体积增大并与饮酒渴望有关(Chung & Clark, 2014)。在灰质方面，一项为期 10 年追踪调查发现：与轻度饮酒者相比，无酒精使用障碍的重度饮酒青少年右侧脑岛灰质体积明显更小 (Heikkinen et al., 2017)。有趣的是，对 3 个神经影像学样本(N = 2423)，跨越儿童或青少年到中年的数据进行分析，发现较小的脑岛体积与样本中酒精使用增加有关，这似乎是遗传

上使饮酒增加的危险因素，而并非饮酒的后果(Baranger et al., 2020)。

在行为成瘾方面，网络游戏成瘾(Internet gaming disorder，IGD)的个体，其左脑岛灰质密度显著降低，右脑岛白质密度显著降低(Lin, Dong, Wang, & Du, 2015)。网游成瘾者脑岛灰质萎缩，与网游成瘾的严重程度呈显著正相关(Weng et al., 2013)。IGD 组的年轻人在双侧脑岛和右侧颞下回的皮质厚度增加，另外，IGD 患者的左岛皮质厚度与症状严重程度呈显著正相关(Wang et al., 2018)。一项对过度使用社交媒体的被试的研究发现，双侧后脑岛的灰质体积与社交媒体成瘾症状呈负相关(Turel, He, Brevers, & Bechara, 2018)。同样，智能手机成瘾（smartphone addiction，SPA）的个体，其左侧脑岛前叶的灰质体积较对照组也有明显降低(Horvath et al., 2020)。

在赌博成瘾研究中，有结果表明，对事件序列的扭曲认知过程可能通常是由脑岛的提供支持的。与赌博相关的认知扭曲程度越高的个体，其右脑岛灰质体积越大(Lu, Kong, & Kong, 2019; Noel, Brevers, & Bechara, 2013)。在健康对照组和其他脑区受损的患者显示出高度的“差点赢（near-miss）”效应并表现出典型的赌徒谬论效应时，脑岛损伤的患者却没有这些行为。减少脑岛反应性的干预措施可能在治疗赌博成瘾方面大有前景(Clark, Studer, Bruss, Tranel, & Bechara, 2014)。

总之，这些证据表明，在成瘾个体中，脑岛的结构发生了变化，且大多数的发现都指向脑岛灰质体积和密度的减少，从而证明了它与成瘾的关系。

2.2 脑岛在成瘾中的功能连接异常

在各类成瘾中，以脑岛为中心的网络功能以及其功能连接总体呈现减弱的特征。吸烟者的右侧前脑岛和右侧额上回之间的静息态功能连接(Resting state functional connectivity ，rsFC)降低(Fedota, Matous, Salmeron, Gu, Ross, & Stein, 2016)。此外，与不吸烟的对照组相比，吸烟者的脑岛与 OFC、额上回、颞叶之间的静息态功能连接明显降低，脑岛和 OFC、颞叶、枕叶之间的静息态功能连接与 FTND 得分呈正相关，而脑岛和前 ACC 之间的静息态功能连接与 FTND 得分呈负相关(Zhou et al., 2017)；在对吸烟者进行戒断尼古丁的研究中发现，复吸组左右脑岛与双侧中央前后回之间的静息态功能连接比未复吸组更弱，表明易复吸性与后脑岛和初级感觉运动皮层之间较弱的连接有关(Addicott, Sweitzer, Froeliger, Rose, & Mc Clernon, 2015)。一项比较吸烟者戒烟 48 小时前后的静息状态血氧水平依赖数据的研究中，将三个右半球脑岛区域（背侧，腹侧和后侧）作为分析的种子点，结果发现，戒烟期间被试的整体动态静息功能连接降低。具体而言，背侧和后侧脑岛与默认模式(default mode)和突显网络的连接增强，而腹侧脑岛与执行控制网络(executive control network)的连接减少。此外，腹侧和后侧脑岛种子点间的静息态功能连接与主观厌恶情绪和戒断症状评分显著相关(Fedota et al., 2018)。一项研究发现，吸烟者风险决策的增加，与更强的尼古丁依赖导致的 dACC-rAI，dACC-lAI 和 rAI-lAI 的 rsFC 增强相关，但与风险水平相关的激活无关 (Wei et al., 2016)。非静息状态的研究也发现，参与了一项涉及吸烟和中性线索的记忆提取任务的吸

烟者，在提取吸烟线索时，左脑岛活动比提取中性线索时更活跃，吸烟者在看到吸烟提示图像时也表现出更强烈的渴望(Janes et al., 2015)。元分析得出结论，与中性线索相比，吸烟线索能在脑岛引起更大的 fMRI 反应(Engelmann et al., 2012)。吸烟线索导致左脑岛与右脑岛、OFC 和纹状体的功能连接更强，且尼古丁依赖评分越高，相关回路间的连通性更强 (Claus, Blaine, Filbey, Mayer, & Hutchison, 2013)。

依赖处方阿片类药物的个体，前脑岛与前中扣带皮层、壳核以及杏仁核的静息态功能连接减弱，且药物使用时间越长,功能连接的变化就越大(Upadhyay et al., 2010)。可卡因使用者的左右脑岛之间以及脑前扣带皮层之间的静息态功能连接降低，从而影响了突显网络(Geng et al., 2017)。对于未复吸组，复吸可卡因的个体其后脑岛与壳核之间的静息态功能连接更弱(McHugh et al., 2013)。可卡因使用者前脑岛和前扣带皮层的静息态功能连接，纹状体之间的功能连接明显较弱,网络间功能连接强度与可卡因使用者更大的非计划冲动显著相关(Wisner, Patzelt, Lim, & MacDonald, 2013)。与安慰剂相比，给予尼古丁时，大脑右侧前脑岛和纹状体区域对奖赏或损失线索的反应也会增强(Moran et al., 2018)。

与对照组相比，酒精成瘾组在纹状体、脑岛和前扣带皮层之间显示出更强的 rsFC(Kohno, Dennis, McCready, & Hoffman, 2017)。与使用安慰剂的对照组相比，经常饮酒的人在饮酒后，其大脑活动与 dACC 之间的连接较弱；此外，酒精越能降低右侧 aINS-dACC 的功能连接，参与者在酒精作用下越平静。这表明突显网络的这两个区域之间的连接减少可能与酒精的奖励效应有关(Gorka, Phan, & Childs, 2018)。酒精使用者在空间工作记忆任务中的突显网络连接低于对照组，脑岛的血流量减少(Sullivan et al., 2013)。

在行为成瘾的相关研究中，也发现了网络游戏障碍被试背侧壳核与后脑岛的功能连接减弱(Hong et al., 2015)，辅助运动皮层与脑岛功能连接减弱(Jin et al., 2016)，与健康被试组相比，IGD 组左后脑岛与双侧辅助运动区、中环带皮层、右后脑岛与右额上回之间的功能连接减弱，脑岛亚区之间的功能整合性降低(Zhang, Mei, Zhang, Wu, & Zhang, 2016)。网络游戏成瘾者在前脑岛和前扣带皮层、壳核、角回网络之间静息态功能连接增强，此外，网络游戏成瘾的严重程度与前脑岛和角回之间的功能连接，以及后脑岛和后脑回之间的功能连接呈正相关关系；网络游戏的持续使用时间与前脑岛和前扣带皮层之间的功能连接呈正相关(Zhang et al., 2016)。另一项研究发现，休闲游戏玩家在面对游戏线索时其壳-额中回-岛叶神经通路呈显著正相关，但游戏成瘾玩家中不存在这种效应，表明 IGD 患者壳核对前额皮质的抑制性神经调节破坏了比较奖励系统(纹状体)、控制系统(前额叶皮层)和内感受知觉系统(脑岛)之间的平衡(Wang, Dong, Zheng, Du, & Dong, 2020)。长时间的睡前使用智能手机会影响睡眠质量和白天的精神状态，研究发现，左侧脑岛与右侧壳核之间、右侧脑岛与左侧额上回、颞中回、梭状回、眶额下回、右侧颞上回之间的 rsFC 强度与睡前使用手机的时间呈正相关(Hobkirk et al., 2018)。

在针对赌博成瘾的静息态功能连接研究中，研究人员发现：没有药物滥用问题的赌博成

瘾患者的脑岛种子点与默认模式网络区连接强度与赌博成瘾程度呈正相关，赌博成瘾患者左脑岛种子与内侧前额叶皮层、双侧颞顶交界处，右脑岛种子与扣带回后部、双侧颞顶交界处的功能连接强度与成瘾程度呈正相关(Kosuke, Toshihiko, Ryosaku, Toshiya, & Hidehiko, 2020)。

综上所述，许多基于静息态脑功能的研究证实了脑岛功能活动的改变与成瘾有关。成瘾导致了突显网络功能和脑岛与执行功能区域的连接性改变。

3. 脑岛与成瘾干预

虽然脑岛参与成瘾的证据是令人信服的，但将其转化为成瘾个体治疗的研究还很缺乏。

深部脑刺激(DBS)可能是一种有效治疗药物成瘾的方法。在过去的 15 年里，已经看到了许多针对各种药物滥用的动物 DBS 研究，大多数报告显示，随着刺激，药物寻求行为有所减少 (Wang, Moosa, Dallapiazza, Elias, & Lynch, 2018)。脑岛区域的刺激显著减弱了大鼠在强化方式下的尼古丁摄入，以及线索和启动诱导的尼古丁寻找行为(Pushparaj et al., 2013)。但目前已发表的关于药物成瘾 DBS 的人类经验仅限于几个有希望的病例系列或病例报告，还需要进一步的动物和人类研究来确定 DBS 在药物成瘾治疗中的作用。

重复经颅磁刺激(rTMS)越来越多地用于治疗药物依赖(Diana, Raij, Melis, Nummenmaa, Leggio, & Bonci, 2017)。一项选取 8 名健康被试的被试内双盲初步研究中，在重复经颅磁刺激(rTMS)下使用磁场线圈法（H-Coil）双侧定位脑岛区域，然后使用正电子发射断层扫描(PET)测量多巴胺水平的变化。所有受试者在 rTMS 前分别接受 3 天的 PHNO-PET 扫描(假刺激, 1Hz 或 10Hz)。结果表明针对脑岛皮层的低频 rTMS (1Hz)显著降低了黑质、感觉运动纹状体和联想纹状体的多巴胺水平。在吸烟者或酗酒者中复制这项研究，将是评估 H-Coil 刺激双侧脑岛是否可以作为成瘾治疗选择的一个合乎逻辑的后续行动(Malik et al., 2018)。

元分析发现，高频 rTMS 对与尼古丁使用障碍相关的渴望有有益影响，但现有的证据并不能充分支持 rTMS 在酒精中毒治疗中的有效性(Maiti, Mishra, & Hota, 2017) 。一项研究招募了每天至少吸 20 支烟且之前治疗失败的成年人(N = 115)，参与者被随机分配到每天接受 13 次高频率、低频率或虚假刺激的实验条件下，这些刺激是在吸烟暗示出现之后或没有出现的情况下进行的，深度经颅磁刺激针对外侧 PFC 和双侧脑岛，采用磁场线圈法（H-Coil）。结果发现高频率深度经颅磁刺激治疗显著减少了香烟消费和尼古丁依赖，然而这项研究并不是专门针对脑岛的，因此无法知道临床效果是由脑岛或 PFC 单独介导的，亦或两者都有(Dinur-Klein et al., 2014)。另一项 56 名酒精依赖患者参加的一个双盲、假对照的随机试验中，参与者接受 10hz 的 rTMS 或假刺激（使用 H8 线圈，每周 5 天，持续 3 周）。刺激目标是脑岛皮层和两侧的覆盖区域，但不包括前额叶。虽然在治疗期间，观察到渴望和饮酒行为明显减少，但在 rTMS 和虚假刺激之间没有差异；两组患者在治疗结束后及 12 周的随访中，饮酒情况均有所增加。总的来说，这项研究并不支持 rTMS 针对酒精成瘾患者的脑岛的疗效(Perini et al., 2020)。

在行为成瘾方面，虽然目前没有针对脑岛的刺激研究，但之前的研究报告 rTMS 和经颅

直流电刺激（tDCS）刺激能减少赌博渴望或赌博相关症状，一项对右侧 DLPFC 使用单一疗程的低频 rTMS 对照的研究发现，rTMS 刺激与赌博冲动的显著减少相关 (Sauvaget et al., 2018)，但 rTMS 刺激对赌博行为本身的减少无效(Rosenberg, Klein, & Dannon, 2013; Sauvaget et al., 2018)；针对 DLPFC 的 tDCS 可以调节赌博障碍患者的氨基丁酸水平(Dickler et al., 2018)，增强了赌博障碍患者的决策能力和认知灵活性(Soyata, Aksu, Woods, Iscen, Sacar, & Karamursel, 2019)。对游戏成瘾被试的 DLPFC 进行重复 tDCS 刺激，降低了游戏成瘾被试的成瘾症状，减少了被试的游戏时间，提高了他们的自我控制能力(Lee et al., 2019)。之前的研究表明，行为成瘾与物质成瘾有着行为和神经生理结果之间的差异 (Gomis, Thoma, Turner, Hill, & Pascual-Leone, 2019)，因此探索行为成瘾特有的认知和神经生理特征，针对与行为成瘾相关的区域，建立单独的脑刺激方法，是值得尝试的领域。

总之，脑岛具有许多与成瘾相关的关键功能，成瘾者的脑岛结构和功能发生了不同程度的改变。大量研究结果表明，脑岛是一个极有希望成为干预成瘾的目标区域。脑刺激技术正在进步，这也从技术层面允许研究者以脑岛为治疗成瘾的方向，为成瘾者提供有前景的治疗结果。

4. 讨论

脑岛在成瘾中的重要作用已经显而易见，但因其结构和功能都呈现出前后异质的分布式特征，必须从其具有功能和结构分化的亚区这一角度进行研究，才能更深入理解脑岛在成瘾中的作用。虽然大多数关于成瘾的发现都指向脑岛灰质体积和脑岛密度的减少，以脑岛为中心的网络功能以及其功能连接总体体现出减弱的特征。但与此同时，也有部分研究发现了相悖的结果，比如，有研究发现，吸烟者左脑岛皮质灰质密度增加 (Zhang et al., 2011)；可卡因使用者的可卡因依赖与右脑岛和背内侧前额叶、额下回、双侧背外侧前额叶之间增强的功能连接有关(Cisler et al., 2013)；与健康控制组相比,海洛因成瘾者大脑左侧岛叶功能连接显著性增强,且与海洛因食用剂量成正相关(陈佳杰等，2017)。

而有关脑岛在这一系列研究中出现的矛盾结果，一方面可能跟脑岛本身所具有的功能和结构异质性有关，脑岛的不同亚区具有不同的功能，并参与不同的功能网络，而上述某些结论相悖的研究并未区分出脑岛的亚区。另一方面，脑岛是一个具有动态功能变化的典型区域，脑岛是内感受的中枢，同时也是对不同网络资源进行调节的中枢，它通过监控内部状态来调节有限认知资源的去向，因此，内感受机制的变化（如是否处于戒断或者渴求状态）对脑岛的功能响应至关重要，上述的研究也未涉及成瘾个体内感受的状态（黄小璐，2018）。此外，不用成瘾的共性和特性，也需要进行考虑，大量研究证明，在成瘾药物作用下，神经系统发生长时程适应性改变是物质成瘾行为形成的基础。而与物质依赖的成瘾行为相比，行为成瘾没有受到任何摄入物质的影响，故其依赖状态的形成主要是心理机制所致。以网游成瘾和海洛因成瘾为例，虽然网游成瘾应该是同海洛因成瘾一样性质的精神病性障碍(都存在脑结构和功能的损害)，但其成瘾程度比海洛因成瘾低(脑损害偏于低级中枢，且范围更小)，经过治

疗康复或者自愈的可能性也较大（贺金波,聂余峰,周宗奎,柴瑶，2017）。即使同为物质成瘾，不同成瘾也具有特异性。虽然特质冲动被认为是物质使用障碍治疗结果的一个良好预测因子(Loree, Lundahl, & Ledgerwood, 2015)，但使用 upps 模型通过紧迫性、缺乏预谋、缺乏毅力和感觉寻求四个方面描述的冲动特征却在不同的成瘾中有所不同。最近的研究表明,高感觉寻求和缺乏毅力与有问题的酒精使用有关(Thomsen et al., 2018)，缺乏预谋可以预测酒精摄入量和酗酒行为，而消极的紧迫感可以预测酒精相关问题(Tran, Teese, & Gill, 2018)，吸烟状态和尼古丁依赖的严重程度与冲动相关的所有特征显著相关，缺乏预谋和积极的紧迫感与吸烟状态的相关性最大($r = 0.20$, $r = 0.24$)(Kale, Stautz, & Cooper, 2018)。此外，在成瘾行为的干预上，不同成瘾也有不同结果，元分析发现，高频 rTMS 对与尼古丁使用障碍相关的渴望有有益影响，但现有的证据并不能充分支持 rTMS 在酒精成瘾治疗中的有效性(Maiti, Mishra, & Hota, 2017)。因此，不同成瘾的共形和特性，还需要通过脑岛的精细分区和明确被试的内感受状态，在今后的研究进一步挖掘。

此外，可以从多种方法结合来考察脑岛在成瘾中的具体作用。如 rTMS 和 fMRI 结合的方法已经被用于抑郁症(Zheng et al., 2020)、帕金森(Bhat et al., 2018)等疾病的研究，通过 fMRI 等手段来观察脑刺激在干预成瘾中对脑岛的具体影响值得尝试。另外，已有研究发现药物诱导的 rsFC 变化与尼古丁戒断密切相关，varenicline 和尼古丁降低了杏仁核-脑岛回路的 rsFC 强度，而在非吸烟者中没有发现类似的作用(Sutherland, Carroll, Salmeron, Ross, Hong, & Stein, 2013)，因此用脑刺激联合药物治疗脑岛成瘾也是可行的思路。

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The structural and functional changes of the insula in people with addiction

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Abstract: Located deep in the lateral sulcus, the insula has a wide range of functions. Existing literature has revealed that structural changes and functional connectivity abnormalities in the insula are associated with addictive behaviors. Therefore, how stimulations in the insula could lead to changes in addictive behaviors becomes the focus of ongoing research. The current paper reviews findings on the structural changes and abnormal functional connections of the insula associated with addiction and summarizes the related studies on insula treatment through brain stimulation intervention. Future studies should investigate the specific roles of subdivisions of the insula in addiction with a combination of multiple methods, further explore the commonality and characteristics of different types of addiction, and eventually lead to more effective intervention programs.

Key words: insula, addiction, intervention, functional connectivity, brain imaging